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HEADLINE: Researchers Claim Embryonic Cell Mix Of Human and Cow

BYLINE: By NICHOLAS WADE

BODY:

Venturing deep into uncharted realms of ethics and medicine, a small biotechnology company said yesterday that its scientists had for the first time made human cells revert to the primordial, embryonic state from which all other cells develop, by fusing them with cow eggs and creating a hybrid cell.

The research comes from biologists who are well known in their field but has yet to be confirmed or published in a scientific journal. Their company, Advanced Cell Technology of Worcester, Mass., said the method could eventually be used to grow replacement body tissues of any kind from a patient's cells, sidestepping the increasing scarcity of organs available for transplant and the problems of immune rejection.

The technique is likely to concern and perplex ethicists because it would involve the creation of an embryonic cell that is part human and part cow, consisting of a human cell's nucleus in a cow egg whose own nucleus had been removed. The company said the hybrid cell quickly became more humanlike as the human nucleus took control and displaced cow proteins with human proteins. Creation of the embryonic cells is an important component of a strategy that in principle offers high medical benefits if it can overcome the high barrier to public acceptance.

The technique would involve creating an embryo of uncertain moral status, and one that crosses the barrier between humans and other species. Even though a hybrid would be in the form of cells, not a whole organism, the concept of half-human creatures arouses deep-seated anxiety, as is evident from the unfriendly powers ascribed to werewolves, centaurs, mermaids, Minotaurs and other characters of myth and folklore.

"Many people are going to be horrified by this scenario, others will say 'So what?' " said Thomas Murray, director of the center for biomedical ethics at Case Western Reserve University in Cleveland and a member of the National Bioethics Advisory Commission. "This is the sort of thing that makes me very uncomfortable," Mr. Murray said. "I think we are likely to get a very powerful reaction to it, and I would like for all of us to have a breathing space here to

articulate our moral concerns."

Another serious uncertainty is the preliminary nature of Advanced Cell Technology's work. No article has yet been submitted for peer review and publication in a scientific journal, an essential touchstone of credibility. Scientists asked about the company's work said they would require much more proof before believing that human embryonic stemlike cells had been created as the company contends, and some were skeptical that the technique would work.

Announcement Tests the Waters

The company said yesterday that it had achieved the feat with one cell almost three years ago. Dr. Michael D. West, Advanced Cell Technology's chief executive, said that he was announcing the work to test its public acceptability. He said the company, which is privately held, was not planning to go public or raise money now but needed to decide whether to commit money to development of the technique.

Some scientists praised Dr. West's decision to make his work public but others were critical, saying he has invited a possibly fraught public debate on a slender basis of fact.

Dr. West is the founder of Geron, a biotechnology company in Menlo Park, Calif., that has had two spectacular successes this year in research on aging. In January it developed a method for "immortalizing" human cells grown in the laboratory by making them leap the supposedly immutable barrier at which cells usually lapse into senescence. Last week two university teams sponsored by Geron said they had isolated and cultivated human embryonic stem cells, the all-purpose cells from which the fetus develops. Dr. West laid the foundations for these developments by sponsoring leading scientists in the two fields.

Researcher Uses His Own Cells

Advanced Cell Technology, which Dr. West joined in October, has focused on cloning and genetically improving cows, a technology developed by James M. Robl and colleagues at the University of Massachusetts at Amherst. Dr. West said he hoped to use the technology to further the idea on which he founded Geron, that of delving into the mystery of human aging and sidestepping some of its processes.

The company said the work with human cells was performed in 1996 by a Jose Cibelli, a colleague of Dr. Robl's at the University of Massachusetts. Using 52 of his own cells, some of them white blood cells and others scraped from the inside of his cheek, Dr. Cibelli fused each one with a cow egg whose own nucleus and DNA had been removed, the company said. Most failed to thrive but one embryo grew and divided five times, generating cells resembling embryonic stem cells. Dr. Cibelli and Dr. West say the method could be made more efficient with present technology. They use cow eggs because these are far cheaper and more available than human eggs and raise no ethical problems.

Considering this work was sufficient to describe an invention, Dr. Robl and Dr. Cibelli filed a patent application and then set the research aside to focus on the more immediately practical field of cow cloning, they said. Only two others beside himself and Dr. Robl knew what had been done, Dr. Cibelli said.

The patent has not yet been issued but Dr. West said he was confident of receiving "important intellectual property" in the field. He said he is making the hybrid cell technique public now "because I want to be very open and level with everyone. We need to get the ethicists to talk about it so as to encourage a rational response to these new technologies."

Dr. Cibelli said he regarded any embryos obtained in this way as "not a separate individual, just a de-differentiated cell from a patient." Differentiation is the process whereby the all-purpose cells of the very early embryo, known as human embryonic stem cells, become committed to their roles as the various specialized tissues of the body. The process is irreversible in nature, but egg cells apparently have the ability to de-differentiate, or reset to default mode, the settings in a specialized cell's nucleus. This is presumably what happened in the experiment reported this July when mice were cloned by transferring the nucleus of an adult mouse cell into another mouse's egg cell.

Dr. Cibelli, who trained as a veterinarian in Argentina, said he believed he and his colleagues "were the first to de-differentiate a human cell by nuclear transfer." Asked if he was concerned about destroying, in principle, potential twins of himself, he said: "I never thought about it, it's a good question. But if you use your own cells to treat a disease you may have, you are not taking cells from another person selfishly."

Dr. West and Dr. Cibelli said they had no intent of transferring the embryos to a uterus, a step considered unethical and unsafe: the embryos would be created solely for the purpose of tissue culture. "Any technology can be abused, but once the public understands how these cells can be used to treat any disease caused by loss or malfunction of cells, from Parkinson's to diabetes to heart disease, the concerns will be overshadowed," Dr. West said.

Lack of Evidence Raises Doubts

Whether Dr. West's prediction will be borne out depends on two major sets of factors, the scientific validity of the proposed method and the ethical and legal questions that related work has already raised.

From discussions with scientists, ethicists and lawyers in the past few days, these concerns have emerged.

Scientists are particularly critical of the lack of supporting evidence accompanying Advanced Cell Technology's announcement, saying in essence the claim could be true but there is no compelling reason to accept it. Even if the claim is valid, biologists note a serious uncertainty relating to an important component of the cells known as the mitochondria, which produce the energy the cell needs and are, in essence, its batteries. If the bovine mitochondria should prove incompatible with their humanized environment, the cells will not be viable.

Ethicists said the mixing of species was likely to trouble the public severely, at least at first. Lawyers who specialize in issues of human reproduction note that the moral and legal status of the human embryo is undecided in American law, a fact pointed up by the isolation of the human embryonic stem cells announced last week. The new entity adds further complexity.

If Advanced Cell Technology can produce viable hybrid cells, they would offer a new route to growing new tissues for transplant. This is the same goal held by the scientists who announced last week that they had grown human embryonic stem cells in the laboratory. It is widely accepted in principle that embryonic stem cells can be directed to develop into any desired tissue, with enormous

potential for medicine, though this has yet to be achieved in practice.

Dr. West said the advantage of the Advanced Cell Technology method is that embryonic cells derived from the patient being treated would generate entirely compatible tissues. The two methods reported last week, by Dr. James A. Thomson of the University of Wisconsin and Dr. John Gearhart of the Johns Hopkins University, derive stem cells from human embryos or fetuses. Tissues made from these cells would be incompatible with the patient, a problem that has not been resolved.

In support of its claim, Advanced Cell Technology supplied a patent application and a photograph taken of its embryonic cells under a microscope. The patent application describes how the cells are made but provides no proof that they possess the properties to be expected of human embryonic stem cells. Dr. Robl said his laboratory was not set up to perform the required tests at the time the hybrid cells were made.

Shown the photograph of the purported hybrid cells, Dr. John Gearhart of Johns Hopkins, author of one of the two methods reported last week, said that "they certainly could be embryonic stem cells" but that no scientific journal would publish the result without further proof. "It's not that I don't believe this biologically, I just think they could have given a little bit more assurance as to what was done here."

Dr. Roger Pedersen of the University of California, San Francisco, who also works on human embryonic stem cells, said he doubted any hybrid cells would last long enough to develop into useful tissue because of their cow-derived mitochondria. The mitochondria of chimpanzees and gorillas work well enough in human cells but those of primate species that diverged more than 10 million years ago from the human line, do not work.

Because cows and humans last shared an ancestor so long ago, cow mitochondria are very unlikely to work well with a human nucleus, in Dr. Pedersen's view, and as most of the mitochondria in the hybrid cells are contributed by the cow egg, the cells would probably not remain viable for long. "It's hard to say this is a total sham, but I smell a sham here," he said.

Citing the same data, Dr. Gearhart said the mitochondria in the hybrid cell had clearly carried it through its first few divisions but might not sustain it in further development, unless the few human mitochondria that were also present somehow took over.

Dr. Pedersen said Advanced Cell Technology should be held to a high standard of proof "because of what the implications are for upsetting people unnecessarily -- if you cry fire in a crowded auditorium you may be liable if it's a false alarm."

New Frontiers For Medical Ethics

The human embryonic stem cells announced last week have already pushed against the frontiers of ethical acceptance. Experts in biomedical ethics say the public is likely to be alarmed by the new technique, particularly because of the mingling of species. Dr. Murray of Case Western Reserve University in Cleveland said that the hybrid embryo "escapes our usual categories." When biologists first learned to transfer genes from one species to another, "The idea of human-animal hybrids was often raised as the kind of monstrosity that no morally perceptive person would ever create," he said.

"Even if it's only to create tissue, the minute you start mixing species you raise all kinds of red flags in people's minds," said Barnie Steinboch, a moral philosopher at the State University of New York in Albany. But she noted that pig valves are now seen as acceptable replacements in human hearts.

Rebecca Dresser, a law professor at Washington University in St. Louis, noted, as did several biologists, that distinctions between humans and other animals are less clear in nature than they are in people's minds. "Biologically a lot of this research is showing us similarities and the upshot in a hundred years may be that the lines between humans and nonhumans will be viewed as a little bit grayer," Professor Dresser said.

A perplexing feature of the hybrid embryo would be that it would start mostly bovine, then become mostly yet not entirely human. But some legal experts have no doubt that any hybrid should be regarded from the start as a human embryo. "It doesn't matter that the mitochondria come from a cow, it also has human mitochondria and so has all the potentials of a human embryo," said Lori Andrews, a professor at the Chicago-Kent College of Law in Chicago.

"Once it's gone through that first division it has gone from being a somatic cell to a thing with potential life," Dr. Andrews said, referring by somatic to the ordinary specialized cells of the human body. If transferred to a woman's uterus the embryos might or might not come to term, "but under state laws it doesn't matter whether the fetus is going to be born or not -- it doesn't make them less human."

The human body consists of 100 billion cells. Should embryos created from them by the cow egg method be regarded as having special status when they can be made so easily and plentifully? Dr. Andrews said that human embryos are not so hard to make the usual way, and the fact that an embryo is easily made, by whatever means, is irrelevant to arguments about its status.

The moral status of the human embryo "is not clearly established in U.S. law," Dr. Dresser said. The embryo can be regarded as mere property, as a person, or as something in between but deserving of special respect. Congress, in banning the use of Federal money for research on human embryos, has favored the view that they are in the category of people. But in custody battles over fertilized embryos, courts have favored the special respect status. Dr. Dresser said the hybrid cells could be seen as between the property and special respect status.

The company said the hybrid cells were made by Dr. Cibelli in Dr. Robl's laboratory in the University of Massachusetts at Amherst. Michael Weinberg,

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executive secretary of the university's human subjects committee, said the experiment was given administrative approval, without review by the committee or major discussion. Dr. Cibelli was using his own cells, not experimenting on other people, and self-experimentation does not require special consent. "If someone wants to inoculate themselves they can do that," Dr. Weinberg said.

CORRECTION-DATE: November 14, 1998, Saturday

CORRECTION:

An article on Thursday about a biotech company's claim to have converted human cells to their primordial state by fusing them with cow eggs misspelled the name of a philosophy professor who said the technique would raise red flags in people's minds. She is Bonnie Steinbock, not Barnie Steinboch.

GRAPHIC: Photo: Michael West, left, Jose Cibelli, center, and Jim Robl at Advanced Cell Technology in Worcester, Mass. The small biotechnology company says it has found a method that may be used to grow human replacement tissue. (Rick Friedman for The New York Times) (pg. A26)

Diagram: "All-Purpose Cells: A Recipe"

Researchers at a company in Massachusetts say they have turned a human body cell back into an embryonic cell, from which all human tissues develop, by fusing the human cell with a cow egg. This is how they say they did it.

1.

Unfertilized eggs are harvested from cows at slaughter-houses.

Cells are taken from inside the cheek of a person.

2.

The nucleus, is removed from the cow egg, leaving its cytoplasm.

3.

The human cell and the cow egg are made to fuse with an electric shock.

4.

In the hybrid cell, the human nucleus begins to direct the cell's functioning.

Primordial cells Dr. Jose Cibelli says he made from a cell of his own.

5.

The result is a cluster of human embryonic stem cells, the kind of cell that gives rise to the vast variety of body tissues.

6

Theoretically, the cells might be . . .

. . . guided into becoming any of the body's tissue types (organs, nerve or bone cells) for transplant-ation.

. . . grown into a clone of their donor, but the company says it would be unethical to do this.

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(Source: Advanced Cell Technology) (pg. A26)

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